

# **EXHIBIT 28**

# Understanding the Rural–Urban Differences in Nonmedical Prescription Opioid Use and Abuse in the United States

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Nonmedical prescription opioid misuse remains a growing public problem in need of action and is concentrated in areas of US states with large rural populations such as Kentucky, West Virginia, Alaska, and Oklahoma. We developed hypotheses regarding the influence of 4 factors: (1) greater opioid prescription in rural areas, creating availability from which illegal markets can arise; (2) an out-migration of young adults; (3) greater rural social and kinship network connections, which may facilitate drug diversion and distribution; and (4) economic stressors that may create vulnerability to drug use more generally. A systematic consideration of the contexts that create differences in availability, access, and preferences is critical to understanding how drug use context varies across geography. (*Am J Public Health.* 2014;104:e52–e59. doi:10.2105/AJPH.2013.301709)

Nonmedical prescription opioid use is a rapidly escalating public health problem. Unintentional overdose deaths from opioid pain relievers has quadrupled since 1999 and by 2007 outnumbered those involving heroin and cocaine combined.<sup>1</sup> Much of this growth has been because of an increased misuse of opioid analgesics, which contributed to 21% of all poisoning deaths in 1999 and 37% in 2006.<sup>2</sup> By 2010, 2.4 million Americans initiated nonmedical prescription opioid use; this equals 6600 daily initiates.<sup>3</sup> Other evidence demonstrates a sharp increase in rates of use of prescription opioids<sup>4,5</sup> abuse or dependence,<sup>4</sup> emergency department visits,<sup>6,7</sup> and overdose injury among all age groups in the United States.<sup>8–10</sup>

Although all states have demonstrated an increase in nonmedical prescription opioid morbidity and mortality during the past decade, death and injury from nonmedical prescription opioid misuse are concentrated in states with large rural populations, such as Kentucky, West Virginia, Alaska, and Oklahoma.<sup>11–13</sup> Distinctions between urban and rural areas are not binary but reflect a continuum of population density and proximity to the 1098 defined metropolitan areas of the United States.<sup>14</sup> We conceptualized rural areas as nonmetropolitan counties, acknowledging that this is a heterogeneous category for geographical areas.

Individuals in counties outside metropolitan areas have higher rates of drug poisoning deaths, including deaths from opioids, and opioid poisonings in nonmetropolitan counties have increased at a rate greater than threefold the increase in metropolitan counties.<sup>11</sup>

Drug related deaths involving opioid analgesics are higher in these rural areas even after adjusting for population density,<sup>15</sup> and the ratio of nonmedical users to medical users is higher in rural areas as well.<sup>16</sup> Nationally representative surveys have indicated that, in rural areas, not only are there higher mortality and injury rates but also adolescents are more likely to use prescription opioids nonmedically than are their urban counterparts.<sup>17–20</sup> These surveys also report that factors such as polydrug use and depression are associated with nonmedical opioid use in rural areas.<sup>20</sup>

Why is nonmedical prescription opioid misuse more prevalent in rural areas than in urban areas? There is, surprisingly, little empirical data that help us address this question. Risk factors that explain rural–urban differences in nonmedical prescription opioid use must vary across rural versus urban geographical contexts and be either associated with drug use generally or use of nonmedical prescription opioids specifically. Although contextual determinants of drug use are important in explaining why individuals use

drugs and become dependent,<sup>21,22</sup> our understanding of the mechanisms through which broadly defined geographical settings influence drug use remains limited.

We approached this issue in 3 steps. First, we explicated an array of known risk factors associated with illicit drug use generally. Second, we considered whether any of these factors are associated specifically with nonmedical prescription opioid use. Third, we linked the factors to the rural context, providing hypotheses that may explain the excess burden of prescription opioid misuse in rural compared with urban areas.

## RISK FACTORS THAT DRIVE ILLICIT DRUG USE

Our model of drug use risk factors is grounded in ecosocial theory and ecological systems theory<sup>21,23,24</sup> and is organized by 3 levels of influence that dynamically interact (Figure 1).

The first is the macro level, where the social context structures the availability of drugs and the norms around use.<sup>25,26</sup> Furthermore, stressors at a macro level such as economic deprivation,<sup>27</sup> inequality,<sup>28</sup> structural discrimination,<sup>29</sup> and other pervasive stressors in the environment may serve as risk factors for drug use.<sup>30,31</sup>

The second is the local context, which includes family dynamics (e.g., supervision, conflict),<sup>32–35</sup> family composition (e.g., older siblings),<sup>36</sup> and family stress (e.g., unemployment). Furthermore, peer influence is a strong correlate of drug use.<sup>37,38</sup>

The third is the micro level. Endogenous factors such as genetic vulnerability,<sup>39</sup> neurobiological factors,<sup>40–42</sup> pharmacological reactivity,<sup>43</sup> personality traits such as sensation seeking and impulsivity,<sup>44,45</sup> psychiatric morbidity,<sup>46–48</sup> and gender and age<sup>49,50</sup> have strong and substantial influences on the propensity to misuse drugs and develop chronic

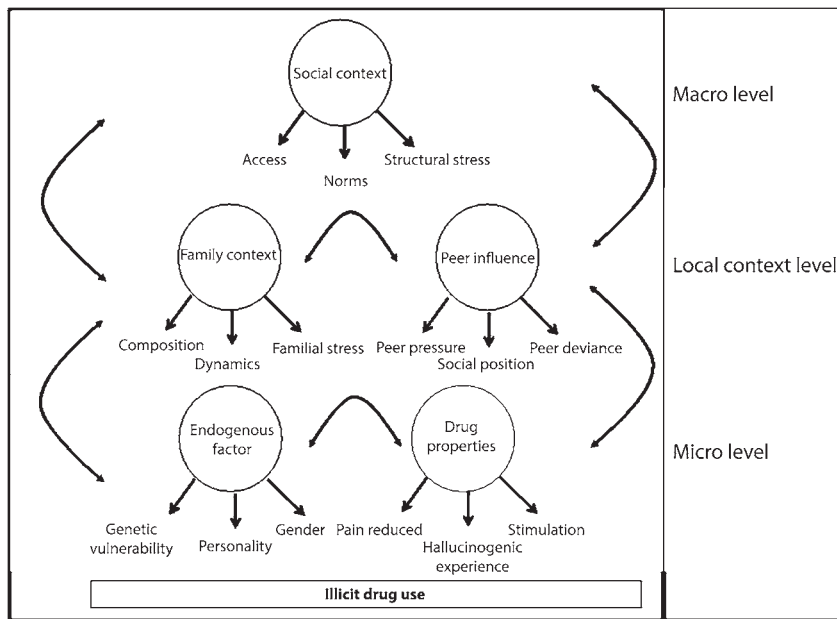


FIGURE 1—A conceptual framework for the etiology of illicit drug use.

drug dependencies. The pharmacological properties of a drug are important in determining who uses them and how they use them.<sup>22</sup>

These 3 levels of influence interact in dynamic ways; for example, social norms regarding substance use, a contextual influence, may affect how peers interact and form relationships around substance use.<sup>51</sup>

## NONMEDICAL PRESCRIPTION DRUGS VS OTHER ILLICIT DRUGS

Many of the well documented risk factors for illicit drug use predict both nonmedical prescription opioid use and other illicit drug use. Therefore, these cannot readily explain why nonmedical prescription opioid use is increasing, especially in rural areas. For example, nonmedical prescription drug users are more likely to be male,<sup>52,53</sup> be young,<sup>54</sup> be polydrug users,<sup>55</sup> have comorbid psychopathology,<sup>54,56–59</sup> and have positive expectations about the effects of use.<sup>60–62</sup> These are all risk factors for illicit drug use more generally. We identified 3 factors for which empirical evidence indicates specificity in association with nonmedical prescription opioid use versus other illicit drugs.

## Increased Availability and Access

Prescription opioids became widely available in the mid 1990s. Between 1997 and 2007, per capita retail purchases of methadone, hydrocodone, and oxycodone increased 13 fold, 4 fold, and 9 fold, respectively.<sup>63</sup> By 2010, enough prescription opioids were sold to medicate every adult in the United States with a dose of 5 milligrams of hydrocodone every 4 hours for 1 month.<sup>64</sup>

A study of national trends found that during 1999 through 2008, overdose death rates, sales, and substance abuse treatment admissions related to prescription opioids increased in parallel.<sup>64</sup> This coincided with a larger movement in the medical community in the late 1990s to identify and treat pain as a fifth vital sign; bodies such as the American Pain Society established guidelines that included aggressive treatment of reported pain, and a campaign initiated by the Department of Veterans Affairs in part fueled the movement with the intention of improving pain management and treating chronic pain.<sup>65–67</sup>

Increased medical use of prescription opioids has resulted in increased access to opioids for nonmedical use, either through the non medical use of legitimately acquired prescriptions or through formal or informal distribution

networks.<sup>68–73</sup> Studies indicate that the large majority of adults who use opioids nonmedically obtain them from friends and relatives or from street level dealers.<sup>68–73</sup> A substantial proportion of overdose deaths and emergency department visits occurs among individuals who have never received a prescription.<sup>10,74–76</sup> The proliferation of illicit high volume prescribers and clinics (so called pill mills) has also contributed to increases in overdoses in states such as Florida and Texas.<sup>18,77</sup>

Although availability of and access to prescription opioids have clearly increased across all areas of the United States, evidence regarding changes in the availability and access of illicit drugs, such as heroin and cocaine, is more mixed. Data on emergency department visits suggest that emergency department visits for prescription opioids more than doubled from 2004 to 2010, whereas cocaine related visits increased 10% and heroin related visits decreased.<sup>78</sup> National survey research indicates no evidence of an increase in the proportion of adolescents and adults who report that drugs such as marijuana are fairly easy or very easy to obtain over the past 10 years<sup>79</sup> (we did not assess comparable data on opioids), suggesting that the availability of nonopioid illicit drugs may not be keeping pace with the availability of prescription opioids, at least among adolescents.

However, data from the National Drug Threat Assessment indicates that heroin and cocaine availability is increasing nationally,<sup>80</sup> although information on comparisons with availability of prescription opioids is not available. Although the available evidence thus suggests that increases in prescription opioid availability have outpaced that of illicit drugs, the nonmedical prescription opioid use epidemic may portend future increases in illicit drug use as well, considering that nonmedical prescription opioid users are more likely than are nonusers to transition to heroin and other illicit drugs.<sup>81</sup>

## Lower Perceptions of Harm

Adolescents perceive prescription opioids such as OxyContin and Vicodin as more harmful than other prescription drugs such as Adderall and amphetamines, but they perceive prescription opioid use as less harmful than the use of almost all other drugs except

experimental alcohol and occasional marijuana use.<sup>82</sup> Lower perceptions of harm for prescription opioids compared with other illicit drugs could be owing to 2 factors.

First, opioid use for pain management is increasingly common; thus, nonmedical users observe and are acquainted with the effective pharmacological action of the drugs among individuals in social and kin networks. Second, prescription opioid use does not necessarily involve routes of transmission with higher social stigma and greater adverse health consequences such as smoking, snorting, and injecting,<sup>83,84</sup> although some evidence indicates that rural nonmedical prescription opioid users are more likely to use nonoral modes of administration than are urban users.<sup>85,86</sup>

### Self-Medicating for Pain

When used as prescribed under medical supervision, opioid analgesics are effective and used as standard practice in managing acute and chronic pain.<sup>87,88</sup>

Because of the fast action in reducing pain and anxiety symptoms, many individuals who overuse legitimate prescriptions or obtain prescription opioids illegally do so to manage existing chronic or acute pain or emotional problems.<sup>89</sup>

### RURAL AREA USE VS URBAN AREA USE

We next considered specific factors that might explain the urban versus rural differences in nonmedical prescription opioid use. We hypothesized that 4 factors might be particularly relevant in explaining these patterns. These hypotheses have an empirical basis but require testing.

### More Increased Availability in Rural Than Urban Areas

Although availability of prescription opioids has increased in all areas, there is evidence that it has increased more in rural areas. Specifically, per capita sales data indicate that states with large rural populations such as West Virginia are among the highest prescribers of opioid analgesics. The data are not entirely consistent with increased availability in rural areas, however, with Florida being a central outlier.

Several nonrural counties in Florida have the highest mean milligrams of opioids dispensed as of 2008,<sup>90</sup> and many of the top prescribing doctors and clinics are in the state of Florida, although recent data indicate that control measures are reducing diversion of and doctor shopping for opioids in Florida.<sup>91</sup> Considering the evidence in total, however, a general picture emerges whereby high prescription rates in many rural counties indicate increased availability in these areas. The marketing of prescription opioids such as OxyContin has been more aggressive in rural communities such as those surrounding Appalachia.<sup>92</sup>

Rural populations are on average older than are urban populations<sup>93,94</sup>; thus, there may be more chronic pain for which management with opioid analgesics is indicated. Furthermore, evidence indicates that chronic pain and injury are more common in rural than in urban areas.<sup>95-97</sup> Finally, qualitative research indicates that prescription drug use in rural areas such as Appalachian Kentucky is an embedded part of the culture of the area, with prescription narcotics often prescribed to maintain a steady workflow in mines and other heavy labor occupations.<sup>98</sup> A higher density of available opioids may create opportunities for illegal markets in rural areas because family and friends are a primary distribution source of nonmedical prescription opioids.<sup>68-73,99</sup>

### Out-Migration of Young People

In the past 2 decades, rural areas have evidenced an out migration of many young adults during peak producing ages. For example, data from the 2010 census indicated that the percentage of individuals older than 65 years in West Virginia (which has a high proportion of rural counties) is twice the percentage of those aged 18 to 24 years (in 1970 the percentages of these 2 age groups were approximately equal).<sup>100</sup>

There are 2 consequences of this out migration that may be related to increases in nonmedical prescription opioid use in rural areas. First is the effect on the economic conditions of the area. Areas with an aging workforce have less new economic infrastructure.<sup>93,101,102</sup> Adverse economic conditions and high rates of unemployment may create greater

vulnerability to drug use in these populations. Second is a selection effect. Young adults who stay in economically deprived areas may have a greater accumulation of risk factors for problematic drug use and may be more likely to have established drug dependencies at a young age that cause downward social drift.

Although data on young adult migration patterns in the United States are scant, substantial research has documented that adolescents in rural areas overall have lower academic aspirations and academic achievement<sup>103,104</sup> as well as fewer returns on academic investment.<sup>103-105</sup> Individuals who have the material resources and aspirations to migrate to urban areas are likely different from individuals who stay on an array of risk factors for drug use, including educational attainment. Data on differences in young adult migration as it relates to risk factors for prescription opioid use are critical for testing and advancing these hypotheses.

### Social and Kinship Networks

The influence of family structures and family life is a central cultural difference between rural life and urban life. Although rural areas are increasingly connected to urban spaces as urbanization continues in the United States, there are substantial differences in social norms, expectations, and cultural values between families of rural versus urban areas.<sup>106-108</sup> For example, in many rural areas a higher value is placed on work and on investment in the community than on education.<sup>109</sup> Individuals in rural areas report knowing the members of their social network longer and being more closely related to members of their social network than are individuals in urban areas.<sup>106</sup> Furthermore, substantial sociological research has documented that individuals in rural areas trust their neighbors more and are more likely to engage socially with neighbors and others who are geographically close.<sup>108,110</sup> Ties to the community are often stronger in rural areas, and greater value is placed on maintaining strong social capital.<sup>107</sup>

In the context of such strong social and kinship networks, economic hardship associated with industrial restructuring and rural to urban migration of youths may generate



strain not only in affected individuals but also in the broader social network, increasing the risk for illicit drug use across the social structure.<sup>107</sup> However, strong social ties with family and community may serve as a buffer against the stress of economic hardship,<sup>111</sup> in which case strong social ties would be associated with reduced drug use in rural areas. Testing and differentiating these pathways are critical for advancing our understanding of rural communities and drug use.

Family structures in rural areas are also larger and fertility rates are higher,<sup>112</sup> suggesting that rural kinship networks are often wider than are urban kinship networks. Substantial empirical evidence indicates that, in contrast to the sources of other illicit drugs, one of the main sources of illicit prescription opioids is the diversion of prescriptions legitimately filled by parents, relatives, friends, or acquaintances.<sup>68–72,99</sup> Thus, family networks matter more for prescription drugs than for other drugs because they are more often obtained from family members, whereas other drugs are more often obtained through friends or the drug trade.

Interestingly, OxyContin use has been significantly associated with increased social capital in rural areas,<sup>113</sup> suggesting that nonmedical prescription opioid distribution networks integrate into social networks in important ways in isolated rural communities. The breadth and proximity of the social network in rural areas may allow faster diffusion of prescription drugs to potential nonmedical users, and sources of prescription opioids through families may be more accessible in rural areas. These wide social networks with close ties across individuals may facilitate the distribution of prescription opioid medication. Little research has mapped social networks of prescription opioid diversion in rural areas; the hypotheses we have outlined provide a road map for addressing the potential differences in diversion and dissemination of prescription opioids in rural versus urban settings.

### Structural Stressors of Modern Rural Living

Although there are stressors associated with living in both urban and rural areas, economic downturns have more adversely affected rural areas in the United States<sup>114</sup>;

thus, stress owing to unemployment and lack of available industry may be more strongly felt in rural areas. It has been well documented that geographical context shapes risk of drug use,<sup>21,22,25,115–117</sup> including poverty and unemployment.<sup>27,28,118–124</sup> Rural counties in particular have faced job sector and industry shifts as populations shift to meet the labor demands of changing markets,<sup>125,126</sup> resulting in long term economic deprivation, high rates of unemployment, and fewer opportunities for establishing a long term career with potential for upward mobility.<sup>125</sup>

Numerous economic analyses have revealed mismatches between the skills of residents and the jobs available to them, and industrial restructuring predicts a shift into poverty of many in the United States.<sup>24,80</sup> Furthermore, in the United States, there have been decreases in the wage rate for low skilled jobs<sup>126</sup> and the demand for manufacturing jobs<sup>127</sup> coupled with an increase in the demand for high skilled workers.<sup>80,86</sup> These factors affect rural more than urban counties,<sup>127</sup> which generally have a greater diversity of labor markets and workers.

### SUMMARY AND FUTURE DIRECTIONS

In the box on this page we have summarized our hypotheses regarding the responsible drivers of the increased prescription opioid misuse in rural areas. We posited that increases could, in part, be attributed to (1) increased sales of opioid analgesics in rural areas that lead to greater availability for nonmedical use through drug diversion networks, (2) out migration of upwardly mobile young adults from rural areas that increases economic

deprivation and creates an aggregation of young adults at high risk for drug use, (3) tight kinship and social networks that allow faster diffusion of nonmedical prescription opioids among those at risk, and (4) increasing economic deprivation and unemployment that create a stressful environment that places individuals at risk for drug use. These factors interact in dynamic ways with identified risk factors that are not unique to nonmedical prescription opioid use to lead to epidemics of prescription opioid use and associated injury in rural areas.

The hypotheses we have proposed do not explain all the observed patterns of nonmedical prescription opioid use and overdose. For example, states such as Florida and Washington have relatively high rates of nonmedical prescription opioid overdose but are largely urban, whereas Iowa and North Dakota have relatively low rates despite substantial rural areas<sup>11,18,128</sup>; thus, the mapping of rural geographical area to increases in nonmedical prescription opioid overdose is not linear.

Furthermore, demographic factors in both urban and rural areas likely interact with the factors we have mentioned in ways that remain to be elaborated. For example, Black and Hispanic individuals face the same if not greater stress because of economic hardship than do Whites and yet have lower overall rates of nonmedical prescription opioid use.<sup>52,53</sup> The intersection of demographic factors such as race and ethnicity with drug and alcohol use remains among the unexplained anomalies in the epidemiological literature on substance use.<sup>129</sup>

Finally, although we focused on prescription opioids, there is growing evidence that the abuse of other prescription drugs such as stimulants and benzodiazepines is also

#### Four Factors That Explain Increases in Nonmedical Prescription Opioid Misuse in Rural More Than Urban Areas

1. Increased sales of opioid analgesics in rural areas lead to greater availability for nonmedical use through diversion.
2. Out migration of upwardly mobile young adults from rural areas increases economic deprivation and creates an aggregation of young adults at high risk for drug use.
3. Tight kinship and social networks allow faster diffusion of nonmedical prescription opioids among those at risk.
4. Increasing economic deprivation and unemployment create a stressful environment that places individuals at risk.

increasing,<sup>57,125</sup> especially among adolescents and young adults.<sup>82</sup> Understanding the distinctions among underlying risk factors for misuse of distinct types of prescription drugs is an important public health priority, as prevention and intervention strategies may differ depending on the type of drug.

The differences in drug use between urban and rural areas are just 1 example of how macrolevel forces shape population level patterns of drug use. A comprehensive understanding of why, for example, rates of alcohol and drug use differ across time, across countries, in countries across states, and across certain population subgroups is critical and understudied. Social norms, cultural traditions, attitudes, availability, and policies are all likely critical to understanding broad differences in prevalence of substance use across areas,<sup>21,36,51,130</sup> yet few efforts have been made to comprehensively collect this information across time and across geographical spaces to examine the influence and the interaction of these factors with more microlevel determinants such as families, peers, and genetics.

We suggest that a strategic comparison between groups with different outcomes is an important way forward for the study of macrolevel influences on substance use. We have demonstrated that comparing urban and rural drug use is one way to find variation in structural factors that affect individual level risk, yet empirical data to test our model remain critical.

National studies with sufficient sample sizes of urban and rural adolescents, young adults, and older adults with information on the economic and social characteristics of geographical spaces such as counties and neighborhoods are needed to advance this literature. Furthermore, the incorporation of novel methods such as agent based or other generative modeling<sup>12,124</sup> would be useful to correctly develop empirical tests in the context of a dynamic social and political space where individuals interact in networks and with their surroundings.

The crisis of nonmedical use of prescription opioids is an important public health priority, and the greatest public health threat remains concentrated in rural, low income areas of the United States. Responding to this

threat requires new theories from which new hypotheses can be developed and new data and methods that can be used to test novel hypotheses. Increased understanding of spatial factors is critical for developing a better model for the etiology of substance use considering the importance of physical setting, as well as for identifying points of intervention and prevention at a population level. ■

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This article was accepted September 21, 2013.

### Contributors

K. M. Keyes drafted the article. M. Cerdá, J. E. Brady, J. R. Havens, and S. Galea drafted specific sections, provided and researched additional sources, and provided critical feedback on all sections of the article. All authors were involved in the development of the conceptual model for the article.

### Acknowledgments

This research was funded by the National Institute of Alcohol Abuse and Alcoholism (grant K01AA021511 to K. M. K.), the National Institute on Drug Abuse (grants K01DA030449 01 to M. C.; R21DA029670 to J. E. B.; R01DA033862, R01DA024598 to J. R. H.), and the Centers for Disease Control and Prevention (grant 1R49CE002096 01 to J. E. B.).

### Human Participant Protection

No protocol approval was necessary because no human participants were involved in this study.

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